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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/027,671	02/23/1998	ALAN K. SMITH	4292-0048-55	3507

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EXAMINER	
SAUNDERS, DAVID A	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 12/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
027,671	SMITH et al
Examiner	**Group Art Unit**
SAUNDERS	1644

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☑ Responsive to communication(s) filed on 2/13/03 & 10/17/03.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☑ Claim(s) 6-8, 10-12, 38-42, 44-45 is/are pending in the application.

Of the above claim(s)_____ is/are withdrawn from consideration.

☐ Claim(s)_____ is/are allowed.

☑ Claim(s) 6-8, 10-12, 38-42, 44-45 is/are rejected.

☐ Claim(s)_____ is/are objected to.

☐ Claim(s)_____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on_____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on_____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number)_____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received:_____.

Attachment(s)

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s)._____

☑ Notice of Reference(s) Cited, PTO-892

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Interview Summary, PTO-413

☐ Notice of Informal Patent Application, PTO-152

☐ Other_____

Office Action Summary

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/17/03 has been entered.

Following entry of the amendment, claims 6-8, 10-12, 38-42 and 44-45 are pending and under examination.

Amendment has overcome the obviously stated rejection under 37 CFR 1.75 (c) and the enablement rejection under 35 USC 112. first paragraph.

The examiner will state 112, first and second paragraph rejections infra, with consideration of the new limitations and applicant's remarks.

Claims 6-12, 38-42 and 44-48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims, when read in light of the specification, are so confusing that the examiner has no idea what is being claimed. Applicant's amended version of claim 38 recites "a lineage committed human hematopoietic cell composition, wherein the lineage committed cells are differentiated at least to a point where they are programmed to develop into a specific cell type", for which applicant indicates support at page 6, lines 18-20. The examiner concurs that these words are literally there and that the applicant uses this phrase to define "lineage committed human cells". However in the remainder

of the paragraph spanning pages 6-7, it appears that applicant has not really limited the lineage committed cells which develop only into one type of cell. Applicant refers (page 6, lines 20-21 to CFU-GEMM cells which develop into mature myeloid cells, and to CFU-L cells which develop into lymphoid cells. Mature myeloid cells develop into numerous types of cells –various granulocytes, macrophages and histocytes; mature lymphoid cells include helper T-cells, cytotoxic T-cells, B-cells, etc; see Clark, Fig.2-1. Thus recitation of "a specific type of cell" at page 6, lines 19-20 encompasses cells which mature into many types. For this reason the examiner considers applicant's urgings that bone marrow stromal cells are "multipotent and can develop into many different types of cells" (response at page 6) to not negate such cells from falling within the ruburic of the "lineage committed human cells" recited in the claim. Since applicant's paragraph spanning specification pages 6-7 considers the "lineage committed human cells" as encompassing anything from "multipotential stem cells or committed progenitor cells" to "mature" or "terminally differentiated" cells, one has no idea what the meets and bounds of the claims are. Further confusion arises from the fact that dependent claim 45 recites "T-cells, dendritic cells or chondrocytes" which exams considers to be terminally differentiated cells; in such case what is meant by the term "lineage committed"?

Applicant's disclosure goes through so many contortions in defining "lineage committed human cells which are differentiated at least to a point where they are programmed to develop into a specific cell type" that it is impossible for the examiner or anyone to understand the claims. If applicant wants to interpret this phrase more

narrowly, he must do more than argue on the record in a manner consistent with the originally filed disclosure. He must recite negative limitations in the claims which rule out what he does not want to claim. Any introduced negative limitation must be supportable by the original disclosure. Ex parte Grasselli 231 USPQ 393.

Regarding claim 45, it is not clear if "chondiocytes" are properly a member of a Markush group of committed hematopoietic cells; please clarify.

In claim 39, line 5 "similar to" is indefinite.

Claim 42 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Amended claim 42 recites new matter by virtue of reciting "further comprise".

Examiner finds no description of a human lineage committed composition of hematopoeitic cells and further comprising the other recited cell types (mesenchymal etc). The original disclosure described hematopoietic cells as being one alternative among the other recited cell types, and there was no particular direction to a combination of hematopoietic cells mixed with one of the other recited cell types.

A new 112, first paragraph rejection is stated infra.

Claims 6-12, 38-42 and 44-45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant was not in possession of his invention at the time of filing.

Applicant's description goes through so many contortions that the examiner has no idea what is being described as noted supra (112, 2nd) recitation of "lineage committed human cells" are "differentiated to at least a point where they are programmed to develop into a specific type of cell" (page 6, lines 18-20) is followed by so many qualifications---i.e. anything from "multipotential stem cells" or "committed progenitor cells" to "terminally differentiated" cells (page 7, lines 2—4)---that the reader has no idea what applicant considers a "lineage committed human cell "may be; a description of everything possible in terms of differentiation states is a description of nothing at all. Applicant has no idea what his invention was when he filed. If applicant wants to describe anything in the claims he must introduce negative language to indicate what his invention is not.

Regarding prior art rejections of record note the following.

Claims 8, 10-12, and 38-40 are rejected under 35 U.S.C. 102(b) as being anticipated by Emerson et al (5,437,994), for reasons of record.

Applicant has urged that the rejection is overcome because the stromal cells are not "differentiated to a point where they are programmed to develop into a specific type of cell. "This does not overcome because, as noted supra under 112 issues, this language is so vague that it is proper for the examiner to consider stromal cells as being encompassed, despite the fact that they may develop into many different types of cells.

The amendment of claim 42 has overcome previously stated rejection of claim 42 over Emerson et al.

Claims 8, 10, 12 and 38-40 are rejected under 35 U.S.C. 102(b) as being anticipated by Caldwell et al (Jour cell physiol 147, 344, 1991) for reasons of record.

This rejection stands for the same reason noted supra regarding Emerson et al.

Rejection of claim 42 has been withdrawn, due to the amendment.

Claims 39-40 have been added to the rejection since GM-CSF is inherently a "cytokine"; see Emerson et al at col.6, line 27.

Claims 6, 10-12, 38-39, 41 and 44-45 are rejected under 35 U.S.C. 102(b) as being anticipated by Freedman et al (Jour Immunol meth 167, 145, 1994), for reasons of record.

Applicant urges that amendment of claim 38 has over come by virtue of reciting "at least 25% daily replacement continuously". This does not. Given the perfusion rate of 60 ml/min or 300 ml/min and a total vol. of 56 liters for the ACSS capillary culture system (page 148, col.2), the rate of exchange would be calculated to be more than "at least 25% daily".

Amendment of claim 42 has overcome the previously stated rejection over Freedman et al.

Claim 44 is included in the rejection since T-cells are from a hematopoietic lineage which is "non-myeloid" and other than stromal".

Claims 8, 10-12, 38-39 and 42 are rejected under 35 U.S.C. 102(b) as being anticipated by Emerson et al (5,437,994).

See infra

Claims 8, 10-12, 38-39 and 42 are rejected under 35 U.S.C. 102(e) as being anticipated by Emerson et al (5,605,822 or 5,635,386 or 5,646,043 or 5,670,147 or 6,326,198).

All Emerson et al references are of the same patent family. Each describes and claims a method of culturing human hematopoietic progenitor cells (which the examiner considers to be encompassed by the claims, given their undefined metes and bounds) in a culture medium, which is replaced at a rate of from 50 to 100 percent per day. See 5,437,994, claim 23; 5,605,822 claims 33-34 and 47; 5,635,386, claims 1 and 53; 5, 646, 043, claims 24, 27 and 34; 5, 670, 147 claim 41; 5, 670, 351, claim 21; and 6,326,198 claim 33. It is to be noted that in stating this rejection the examiner considers "hematopoietic progenitor cells" to be at a more committed stage than are hematopoietic stem cells. See '994 at col.1, lines 22-42.

It is further noted that, irrespective of whether or not any of the cited references show any "enhanced biological function" as a consequence of such culturing conditions, the recited enhancement would have been inherently obtained by Emerson et al. Since applicant's disclosure is so general as to how "enhanced biological function "may be obtained, and since the disclosure has considered medium exchange to be the essential feature which brings about such "enhanced biological function; the examiner considers that applicant has done nothing that Emerson et al did not do. That applicant might have realized same inherent advantage would be obtained by practicing Emerson

et al's method of medium exchange does nothing to overcome anticipation by inherency.

Regarding instant claim 8, note '994 at col.6, lines 1-5; '822 at claims 34 and 47; '386 at claims 1 and 53, part (ii) of each; '043 at claims 24, 27 and 34; '147 at claim 41; '198 at col.6, lines 19-29.

For instant claim 10 see '994 at col.17, line 17 col.18, line 22; '386 at col.33, lines 42-66; '043 at col. 19, line 65-col. 20, line 41; '147 at col.21, lines 22-35; '198 at col.21, lines 33-47.

Regarding instant claim 11 note pat '994 at claims 30-37; '386 at claim 1; '043 at claims 37-43; '147 at col.6, lines 5-29; '198 at claims 43-47.

With respect to instant claim 12 see '994 at col.18, lines 38-61; '386 at col. 34, line 65-col.35, line 18; '043 at col. 21, line 53- col.22, line 17; '147 at col.22, lines 46-67; '198 at col.22, line 65-col.23, line 20.

Regarding instant claim 39, note '994 at col.18, line 62-col.20, line 34, which teach enhanced production of granulocyte-macrophage progenitor cells and which teach that taught culture conditions provide "more effective reconstitution of bone marrow ex vivo". Likewise see '386 at col.35, line 19-col.36; line 30; '043 at col.22, line 18-col.23, line 28; '147 at col.23, line 1-col, 24 line 2; '198 at col.23, line 21-col 24, line 51.

For instant claim 42, '994 teaches that bone marrow stromal cells may be present in the culture (col.7, line 55-col.8, line 12); stromal cells are a type of "mesenchymal cell" (see instant specification page 7). Likewise note '822 at claims 33

and 47; '386 at col.10, lines 28-51; '043 at col.7, lines 31-53; '147 at col.7, lines 30-54; '198 at claim 33.

Claims 10, 12, 38-39 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schneider et al (Jour Immunol meth, 129, 251 1990---ref P Z) in view of Kuauda et al (5,521,085).

Schneider et al teach that, for culturing hybridoma cells producing monoclonal antibodies, an exchange/perfusion rate of 40% per day is optimal for cell growth and antibody production. A hybridoma cell is considered to be terminally differentiated or mature (as set forth at instant specification page 7, lines 3-4). Due to the confusing manner in which applicant's specification defines lineage committed cells (para. Spanning pages 6-7) it is proper for the examiner to consider hybridoma cells as "lineage committed". Schneider et al do not compare 40% exchange against 0% exchange (static culturing); however they do compare against 20%, which is shown to be less than optimal. By extrapolation back to 0%, this would be even less optimal than 20%.

Regarding claim 44, B-cells are from a hematopoietic lineage which is "non-myeloid".

Schneider et al teach all aspects of the instant invention except that the hybridoma cells are murine, rather than human. Fukuda et al teach that it is known to use transformed human B-cells or human-human hybridomas to produce human monoclonal antibodies.

They teach use of static cultures for the production phase e.g. col. 23, line 35; col.24, line 47; col. 49, line 23). From the teachings of Schneider et al one would have expected that, when media exchange culturing is employed in liers of static culturing, one would gain the advantage of increasing antibody production by the human cells of Fukuda et al. Schneider et al teach 40% exchange and one would have reasonably expected this exchange rate to be in the ball park for what is optimal for a wide range of B-cells, whether murine or human.

In summary, the examiner is so confused by the diffuse nature of applicant's disclosure that it is not clear what is to be examined, other than the exchange rate of "at least 25%". Therefore the examiner has cited various references supra that show culturing of hematopoietic cells at various stages—all the way from progenitor cells (Emerson et al) to terminally differentiated B-cells (Fukuda et al). Any reference showing or motivating rapid exchange of the culture media, whether intermittently or continuously, is applicable to the claims and, in the case of patent references, raise an issue of potential interference.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Saunders, PhD whose telephone number is (703) 308-3976. The examiner can normally be reached on Monday-Thursday 8 am - 5:30 pm and on Alternative Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

David A Saunders

DAVID SAUNDERS
PRIMARY EXAMINER
ART UNIT ~~182~~ 1644

Saunders/tgd

December 18, 2003